Clinical Case Report

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Tenofovir alafenamide nephrotoxicity in an HIV-positive patient

A case report

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Abstract

Rationale: Tenofovir alafenamide (TAF) is novel prodrug of Tenofovir, a nucleotide reverse transcriptase inhibitor. TAF is less nephrotoxic than its predecessor prodrug, tenofovir disoproxil fumarate (TDF). Tenofovir causes mitochondrial dysfunction and tubular injury when there is elevated accumulation in proximal tubule cells. TAF's unique pharmacokinetic profile enables provision of lower required doses for antiviral efficacy. Lower concentrations reach renal tubules minimizing intracellular accumulation and mitochondrial damage. TAF has not been associated with the histologic markers of tenofovir-associated nephrotoxicity that are seen with TDF, such as dysmorphic mitochondria in proximal tubule cells. Here, we report a patient with dysmorphic mitochondria on kidney biopsy after initiating therapy with TAF.

Lessons: This case suggests that at risk individuals may experience tubular mitochondrial injury from lower concentrations of tenofovir with TAF.

Abbreviations: eGFR = estimated glomerular filtration rate, HCV = hepatitis C virus, HIV = human immunodeficiency virus, PTC = proximal tubule cell, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, TFV = tenofovir.

Keywords: HIV, proximal tubule injury, tenofovir alafenamide, tenofovir nephrotoxicity

1. Introduction

Tenofovir alafenamide (TAF), a prodrug, is a novel nucleotide reverse transcriptase inhibitor that has efficacy similar to that of tenofovir disoproxil fumarate (TDF) but improved safety profile. In comparison with TDF, TAF contains a phenol and an alanine isopropyl ester, resulting in enhanced stability in plasma. Pharmacokinetic studies have shown that administration of TAF is associated with significantly lower plasma concentration of its metabolite, tenofovir (TFV), compared with TDF. TDF-associated nephrotoxicity is proportional to plasma TFV exposure, and thus, TAF may result in less nephrotoxicity. Mitochondrial dysfunction in proximal tubule cells (PTC) is a hallmark of injury from TDF and has not been described after exposure to TAF. Here, we present a patient who was prescribed TAF and incurred subsequent acute kidney injury with a multifactorial etiology. The biopsy revealed proximal tubule mitochondrial distortion similar to that seen from TDF.

2. Methods

Informed consent was obtained from the patient.

3. Case report

A 58-year old black male presented with volume overload, confusion, and oliguric acute kidney injury. Past medical history included poorly controlled HIV, hepatitis C virus (HCV) complicated by cirrhosis, active heroin and cocaine abuse, and type 2 diabetes. He had been exposed to a TDF-containing regimen approximately 2 years previously. At that time serum creatinine increased from 0.7 mg/dL to 1.3 mg/dL (ref 0.6–1.3 mg/dL), and then decreased to 0.9 mg/dL with TDF cessation. Eight weeks prior to presentation, he was started on emtricitabine-tenofovir alafenamide (Descovy) and coformulated darunavir with cobicistat (Prezcobix). At that time serum creatinine was 0.9 mg/dL, the urine protein-to-creatinine ratio was 0.27 g/g (ref 0.00–0.19 g/g), absolute CD4 count was 367/mm^3 (ref 458–1344/mm^3), and HIV viral load was 14,000 copies/mL (ref <20 copies/mL). Home medications included rifaximin, lactulose, nifedipine, pantoprazole, furosemide, insulin, aspirin, and atorvastatin. He was hemodynamically stable but had labored breathing with bibasilar rales, ascites, and anasarca.

Initial labs showed elevated serum creatinine to 1.5 mg/dL, and the urine protein-to-creatinine ratio to 2.48 g/g. Additional data was notable for C3 43 mg/dL (ref 79–152 mg/dL), C4 12 mg/dL (ref 12–42 mg/dL), IgG 2070 (ref 751–1560 mg/dL), IgA 175 mg/dL (ref 82–453 mg/dL), albumin 1.5 g/dL (ref 3.5–5.3 g/dL), 24 hour urine protein 8540 mg (ref <100 mg/24 hours), urine protein electrophoresis with gamma spike of 5.40 mg/dL, serum

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protein electrophoresis with gamma spike of 0.35 g/dL, kappa/lambda ratio 3.34 (ref 0.26–1.65), and cryoglobulin consisting of monoclonal IgG kappa and polyclonal IgG, IgM, kappa and lambda. Hepatitis C viral load was 1,020,000 IU/mL (ref <15 IU/mL), and hemoglobin A1c was 8.3% (ref 4.5–6.1%). Antinuclear antibody, antineutrophil cytoplasmic antibody, and hepatitis B virus serologies were negative. Urinalysis contained >500 mg/dL glucose (ref negative, serum glucose at that time was 292 mg/dL), 2+ protein, 5 RBC/high power field, and 1 WBC/high power field. Urine sediment analysis revealed granular and tubular epithelial cell casts. Renal ultrasound demonstrated 12.5 cm symmetric kidneys, with normal blood flow and echogenicity, and without hydronephrosis.

A urinary Foley catheter was placed and medical diuresis was attempted, but the patient developed progressive oliguria and creatinine rose to 4 mg/dL. He was started on dialysis for solute control and volume removal. A percutaneous kidney biopsy was obtained on day 14.

4. Kidney biopsy

The biopsy sample contained 33 glomeruli, of which 6 were obsolescent. Notable findings on light microscopy included nodular mesangial expansion, focal glomerular hypercellularity with endocapillary neutrophils, and scattered spikes and holes along the glomerular basement membrane (Fig. 1A and B). There was tubular atrophy and interstitial fibrotic expansion involving approximately 30% of the cores. Also, noted was focal tubular hypertrophy with extensive cytoplasmic vacuolization (Fig. 1C and D) that ultrastructurally showed autophagosomes (Fig. 1E). Several tubular epithelial cells also demonstrated enlarged variably sized mitochondria with abnormal shapes and incomplete cristae (Fig. 1F). Immunofluorescence showed granular mesangial and capillary wall staining for IgA, IgM, and C3 (Fig. 1G and H). Electron microscopy showed scattered mesangial and subendothelial electron dense deposits, rare sub-epithelial electron dense deposits, and over 80% foot process effacement (Fig. 1I and J).

5. Discussion

Here, we present the biopsy findings of a patient on TAF that showed evidence of mitochondrial dysfunction from tenofovir. Although proximal tubule mitochondrial dysfunction is a hallmark of TDF, this is the first time it has been described after exposure to TAF.

TDF is a nucleotide reverse transcriptase inhibitor that is a first-line treatment of HIV, pre-and post-exposure HIV prophylaxis, and chronic hepatitis B infection. TFV is the active metabolite responsible for the nephrotoxicity that occurs in up to 15% of individuals after 2 to 9 years.[1] TDF is rapidly hydrolyzed to TFV after intestinal absorption necessitating larger doses for effective viral control. TFV then undergoes glomerular filtration and active secretion by renal proximal tubule cells (PTC) via the organic anion transporter pathway.[2] With accumulation in renal PTC, TFV alters DNA expression of endothelial nitric oxide synthase, the sodium-phosphorus cotransporter, sodium/hydrogen exchanger 3, and aquaporin 2.[3] This leads to intense renal vasoconstriction, phosphaturia, proximal tubular acidosis, polyuria, and impaired urine concentrating ability.[3–6] TFV accumulation has also been associated with altered mitochondria DNA, which is reflected histologically in dysmorphic and enlarged mitochondria under electron microscopy.[7,8] Chronic exposure to TDF has been associated with 34% increased risk of proteinuria, 11% increased risk of rapid decline, and 33% increased risk of chronic kidney disease.[6]

A novel prodrug, TAF is promoted as a less nephrotoxic alternative to TDF.[9] TAF is metabolized into TFV by hepatocytes and mononuclear cells. This provides prolonged stability in plasma at lower administered doses, less PTC exposure, and reduced risk of accumulation.[2] In randomized controlled trials comparing TAF to TDF, TAF shows similar antiviral efficacy with smaller reductions in eGFR, and less proteinuria, albuminuria, and urine biomarkers (retinol-binding protein and beta-2 microglobulin).[9] Preliminary studies also suggest it is beneficial in patients with chronic kidney disease. In a single-arm, open-label study, Pozniak et al switched virologically suppressed individuals with moderate renal impairment (creatinine clearance 30–60 mL/min) to a TAF-containing regimens and found significant improvements in participants' overall proteinuria, albuminuria, and tubular proteinuria.[10] The use of TAF is increasing given these promising findings.

The kidney biopsy findings demonstrated multiple injuries including evidence of diabetic nephropathy, focal glomerular hypercellularity (Fig. 1B), immune complex deposition (Fig. 1I) and mitochondrial injury. Mesangial expansion (Fig. 1A) with podocyte effacement (Fig. 1J) points to long-standing diabetes and correlates with nephrotic range proteinuria. The immune deposits are potentially driven by uncontrolled HIV and/or chronic HCV. It is the tubular injury that provides new insight for the HIV population. On light microscopy, there is significant proximal tubule hypertrophy, tubule atrophy, and extensive vacuolization. Electron microscopy shows autophagosomes, and mitochondria of variable sizes, shapes, and incomplete cristae (Fig. 1E and F). Dysmorphic mitochondria are characteristic of tenofovir nephrotoxicity that is seen with TDF. Although it is less likely that TFV was responsible for this patient's acute kidney injury, the biopsy indicates that there is sufficient TFV accumulation to cause mitochondrial dysfunction. This is the first time such morphological changes in PTC mitochondria architecture have been described after exposure to TAF.

The crux of this case is whether TAF is responsible for the dysmorphic mitochondria seen in PTC. Risk factors for tenofovir nephrotoxicity include pre-existing kidney disease, diabetes, co-infection with HCV, old age, low body weight, and low CD4 count.[11] Previous exposure to TDF and genetic polymorphisms in cellular transporters also increase susceptibility to tenofovir nephrotoxicity.[11] Ongoing renal impairment results in higher levels of TAF and potentially increased PTC exposure to TFV in this patient.[12] Concurrent diabetic kidney disease, also shown to alter proximal tubule mitochondria, may actually be responsible for these findings.[13] Alternatively, diabetic nephropathy increased the patient's susceptibility to injury from another mitochondrial toxin. This could reflect prior TDF exposure, although this is less likely given the rate of epithelial cell turnover in the proximal tubules and the temporal relationship between the biopsy and TAF initiation.[7] Other causes for these ultrastructural changes, such as adefovir exposure and inherited mitochondria DNA mutations, were not identified in this patient.[7] However, this case raises a concern for potential mitochondrial injury from TAF in patients with known risk factors for tenofovir-associated nephrotoxicity.

In this patient TAF was substituted with a regimen that did not contain TFV. His renal function recovered and he was off dialysis prior to hospital discharge 37 days later. It is the recovery of renal function that suggests TAF-induced renal injury. Four weeks

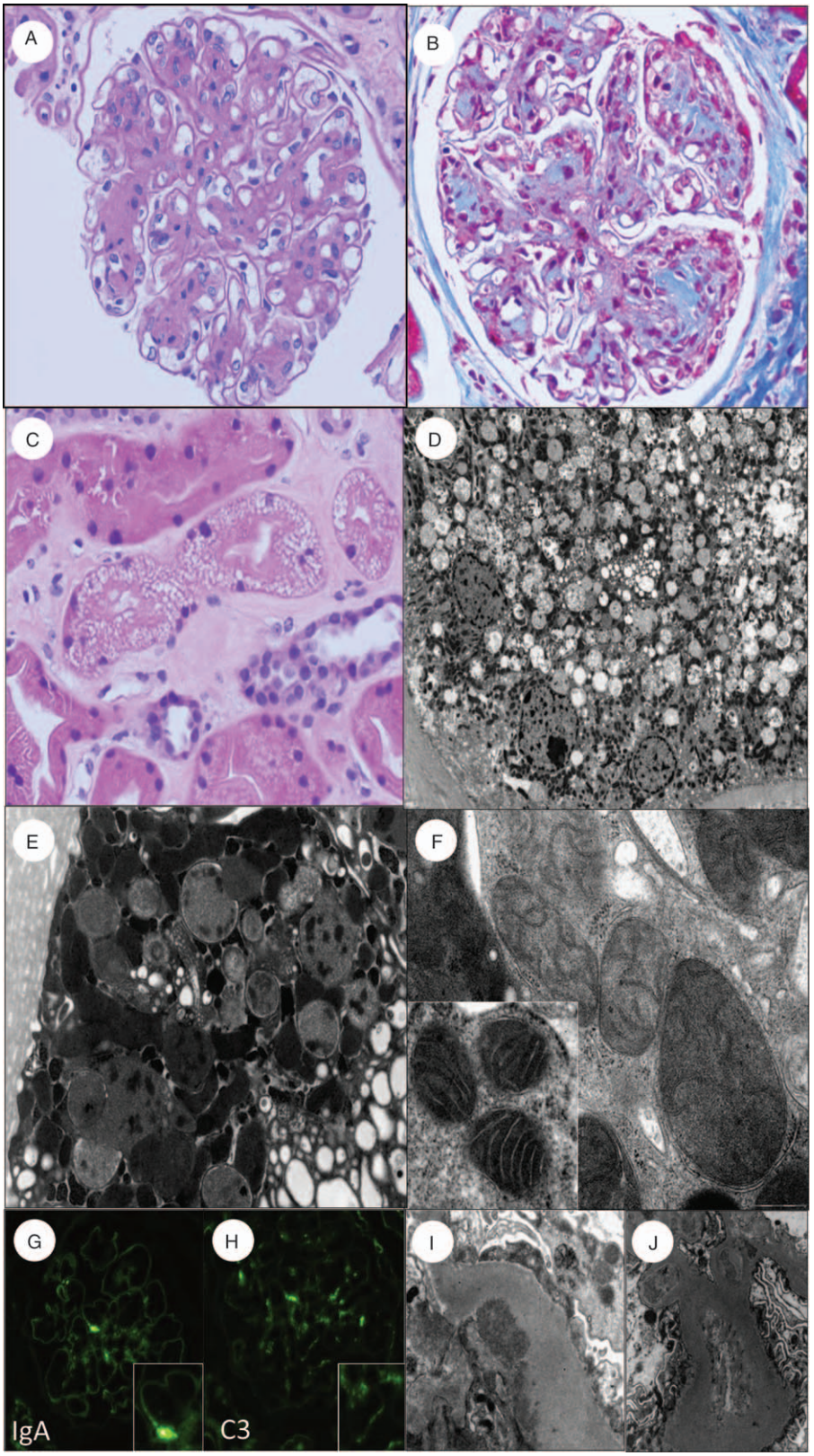

Figure 1. Biopsy findings. There is mesangial expansion with peripheralized thickened capillary loops consistent with diabetic nephropathy and segmental endocapillary leukocytes (A, B). Tubular epithelial vacuolization is observed on (C) routine H&E stain (D) ultrastructure (E) with numerous autophagosomes. Several tubular epithelial cells were dysmorphic mitochondria with incomplete cristae (F) (normal mitochondria, inset).

after drug cessation his serum creatinine was 0.9 mg/dL, and the urine protein-to-creatinine ratio improved from 2.48 g/g to 1.15 g/g. Clearly, the histological changes of diabetic nephropathy and immune deposits potentially driven by HIV and/or HCV are characteristically of chronic nature and unlikely to have vanished if an additional kidney biopsy is to be repeated. In this context, diabetic nephropathy and immune complex disease are less compelling causes of this patient's acute decline in the renal function and is more consistent with drug-induced AKI. Studies on the evolution of renal dysfunction after TDF cessation are inconclusive. The majority of patients show improvements in proteinuria and eGFR, but individuals may be at increased risk for future CKD and proximal tubular dysfunction.[14] The sequelae of renal injury related to TAF is unknown at this time; however, our findings are in line with what is observed for TDF.

Overall, data on TAF suggest improved renal outcomes for individuals with HIV. However, this case calls for increased vigilance in high-risk patients who may suffer mitochondrial injury from TAF under certain conditions.

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